FORM PTO-1390 (REV 11-98) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: Beiersdorf 569-WCG

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/367748

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/00991	20 February 1998 (20.02.98)	21 February 1997 (21.02.97) 20 March 1997 (20.03.97)

TITLE OF INVENTION: PREPARATIONS FOR THE TREATMENT OF ROSACEA

APPLICANT(S) FOR DO/EO/US: Walter DIEMBECK, Udo HOPPE, Birgit SALZER, Gerhard SAUERMANN, Voler STEINKRAUS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

a) Copy of first page of published application WO 98/36730
b) Certified Copy of Priority Documents 197 06 581.3 and 197 11 565.9

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/367748	PCT/EP98/00991	Beiersdorf 569-WCG

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	17 - 20 =	--	X $18.00	$
Independent claims	3 - 3 =	--	X $78.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$
TOTAL OF ABOVE CALCULATIONS =				$
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				$ 840
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 840
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$ 840
			Amount to be: refunded	$
			charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 19-3869 in the amount of $ 840 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-3869. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

SPRUNG KRAMER SCHAEFER & BRISCOE
William C. Gerstenzang
660 White Plains Road
Tarrytown, New York 10591-5144
U.S.A.

SIGNATURE

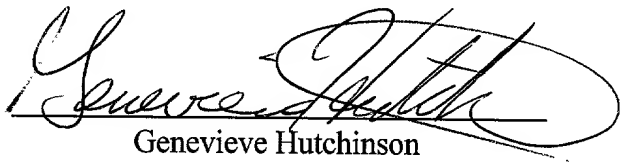
William C. Gerstenzang
NAME

27,552
REGISTRATION NUMBER

"EXPRESS MAIL" mailing label

NUMBER EL457085503US
DATE OF DEPOSIT August 19, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

BY: 
Genevieve Hutchinson

Beiersdorf 569-WCG:pa
6713-Dr.Lt-ka

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Walter DIEMBECK, Udo HOPPE, Birgit SALZER, Gerhard SAUERMANN, Volker STEINKRAUS
PCT Application No.	:	PCT/EP98/00991
Serial No.	:	To be assigned
Filed	:	To be assigned
For	:	PREPARATIONS FOR TREATING ACNE ROSACEA
Art Unit	:	To be assigned
Examiner	:	To be assigned

August 19, 1999

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

In advance of prosecution, kindly amend the above-identified application as follows and consider the following remarks:

IN THE SPECIFICATION

Page 25, please cancel the heading "Patent Claims".

Same page, before claim 1, please insert the heading -- We claim --.

IN THE CLAIMS

Claim 1 (amended) . [Use of] A method for the prophylaxis and treatment of rosacea and couperose which comprises applying to a patient in need thereof an effective amount of one compound or two or more compounds [chosen] selected from the group consisting of NO-synthase inhibitors and derivatives thereof [for the prophylaxis and/or treatment of rosacea and couperose].

Claim 2 (amended). [Use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.] The method of claim 1, wherein said compound or compounds are applied in the form of a cosmetic or dermatological topical preparation.

Claim 3 (amended). Cosmetic or dermatological topical preparations [with] comprising a content of one compound or two or more compounds [chosen] selected from the group consisting of NO-synthase inhibitors and derivatives thereof.

Claim 4 (amended). [Use] Method according to Claim 2, [characterized in that] wherein the preparations comprise at least one antioxidant.

Claim 5 (amended). [Use] Method according to Claim 2, [characterized in that] wherein the preparations comprise at least one UVA filter, [and/or] at least one UVB filter, [and/or] at least one inorganic pigment or a combination of both.

Claim 6 (amended). [Use] Method according to Claim 2, [characterized in that] wherein the preparations comprise at least one antioxidant and at least one UVA filter, [and/or] at least one UVB filter, [and/or] at least one inorganic pigment or a combination thereof.

Claim 7 (amended). [Use of] Method according to claim 1, wherein said one compound or two or more compounds [according to Claim 1, chosen] is selected from the group consisting of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof[for the prophylaxis and/or treatment of rosacea and couperose].

Claim 8 (amended). [Use of cosmetic or dermatological topical preparations] Method according to Claim 2, [with a content of one] wherein said compound or [two or more] compounds [chosen] are selected from the group consisting of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof [for the prophylaxis and/or treatment of rosacea and couperose].

Claim 9 (amended). Cosmetic or dermatological topical preparations according to Claim 3, [with a content of one compound or two or more compounds chosen] wherein said NO-synthase inhibitors and derivatives are selected from the group consisting of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof.

Claim 10 (amended). [Use or preparation] Preparation according to [Claims 7-9, characterized in that] claim 9, wherein said compound is N^G-nitro-L-arginine methyl ester or N^G-nitro-L-arginine methyl ester hydrochloride [is used].

Claim 11 (amended). [Use] Method according to Claim 8, [characterized in that] wherein the preparations comprise at least one antioxidant.

Claim 12 (amended). [Use] Method according to Claim 8, [characterized in that] wherein the preparations comprise at least one UVA filter, [and/or] at least one UVB filter, [and/or] at least one inorganic pigment or a combination thereof.

Claim 13 (amended). [Use] Method according to Claim 8, [characterized in that] wherein the preparations comprise at least one antioxidant and at least one UVA filter, [and/or] at least one UVB filter and/or at least one inorganic pigment or a combination thereof.

Claim 14 (amended). [Use of one compound or two or more compounds chosen from the group of] Method of claim 1, wherein said NO-synthase inhibitors [which] contain an arginine radical[, and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose].

Claim 15 (amended). [Use of] Method of claim 14, wherein said compounds are applied in the form of cosmetic or dermatological topical preparations [with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors which contain an arginine radical, and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose].

Claim 16 (amended). Cosmetic or dermatological topical preparations according to claim 3, wherein said [with a content of one compound or two or more compounds chosen from the group of] NO-synthase inhibitors [which] contain an arginine radical[, and derivatives thereof].

Claim 17 (amended). NO-Synthase inhibitor [containing] having one or more acylated amino groups[, in particular monoacylated amino groups].

REMARKS

This Preliminary Amendment is being filed to eliminate multiple dependency and to place the claims in U.S. conventional format.

Favorable action is respectfully solicited.

Respectfully submitted,

SPRUNG KRAMER SCHAEFER & BRISCOE

By ____________________
William C. Gerstenzang
Reg. No. 27,552

660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

Beiersdorf Aktiengesellschaft
Hamburg

Description

Preparations for the treatment of rosacea

The invention relates to topical cosmetic or dermatological preparations which are suitable for the treatment of rosacea. Here, rosacea also includes the symptoms of couperose.

Rosacea is an inflammatory disease, mainly of the face, which is accompanied with marked erythema, which lasts for a varying length of time, papules and pustules. Telangiectasis and elastosis are frequent, and the intrafollicular accumulation of neutrophils is also observed. Rosacea patients have skin which is extremely sensitive to chemical toxins and physical stress factors (UV light). The pathogenesis is unclear.

Rosacea is incurable, but can be treated with antibiotics, isotretinoin, fungicides such as metronidazole or betablockers.

In contrast to many skin diseases which are associated with a massive influx of leucocytes, leucocyte infiltration in the vicinity of blood vessels and sebaceous glands is moderate.

The question of whether the difficult-to-treat erythema in rosacea patients could be reduced using NO-synthase inhibitors has already been raised in the literature (Qureshi, A.A. et al; Arch. Dermatol. Vol. 132, Aug. 1996, 889-893). An answer, however, has not been given.

Only in the advanced stages of rosacea do telangiectases, papules, pustules and growths such as rhinophyma appear in addition to the differingly developed erythena. These symptoms are treated using surgery.

Overall, the success of the pharmacological treatment of rosacea is unsatisfactory.

The object of the invention was therefore to provide a remedy in this respect and, in particular, to provide active ingredients and preparations with which rosacea, in particular the early stages of this disease, can be treated safely and free from side effects.

These objects are achieved according to the invention.

The invention provides the use, in particular topical use, of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention also provides the use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention further provides cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof.

Suitable NO-synthase inhibitors are, for example,
2-iminobiotin,
L-N^5-(1-iminoethyl)-ornithine (L-NIO),
S-methylisothiourea
S-methylisothiourea sulphate (SMT),
S-methyl-L-thiocitrulline,
L-N^G-(1-iminoethyl)lysine (L-NIL),
7-nitroindazole (7-Ni),
S,S'-1,3-phenylenebis(1,2-ethanediyl)bisisothiourea (NITU)
L-thiocitrulline (2-thioureido-L-norvaline)
and derivatives thereof and, in particular, arginine derivatives.

Preference is given to NO-synthase inhibitors which contain a guanidine group.

Suitable derivatives are, for example, the compounds according to the invention which are monoalkylated or dialkylated on the imino groups or amino groups.

In each case, the alkyl radicals of the monoalkyl groups or dialkyl groups can have from 1 to 10, preferably from 1 to 6, but in particular 1, 2 or 3, carbon atoms, and can be straight-chain or branched.

Also highly suitable are derivatives, in particular of arginine, whose amino groups are completely or partially acylated. These are, in particular, the amino groups of the amino acid radical and, in particular, the amino groups bonded to the alpha-carbon atom. Preference is given to the monoacyl compounds of the active ingredient according to the invention, in particular of an arginine derivative.

A preferred acyl radical is alkylcarbonyl, which is obtained in acylations with carboxylic acids or derivatives thereof, e.g. acid chlorides or anhydrides. The acyl radical or alkylcarbonyl radical can have 2-12, in particular 2-6, carbon atoms and is particularly preferably acetyl.

The compound alpha-N-acetyl-N^G-nitro-L-arginine methyl ester (alpha-N-acetyl-L-NAME), in which the amino group of the alpha-carbon atom of the amino acid function is monoacetylated, is particularly preferred.

The acyl derivatives are characterized by good effectiveness, storage stability and their stability in preparations.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of carboxylic acid groups of the compounds according to the invention with alcohols are also preferred.

Preferred salts are water-soluble salts, e.g. sodium, potassium and ammonium salts. This is also true for the acid addition salts. Suitable acid addition salts are, for example, obtained using inorganic and organic acids. Preference is given to the hydrochlorides, phosphates, sulphates, acetates, caprylates, citrates, lactates, maleates or tartrates.

Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably with monoalcohols. They can be straight-chain or

branched and have, for example, from 1 to 12, preferably from 1 to 6, carbon atoms. Preference is given to methanol, ethanol, n-propanol and isopropanol.

The esters are particularly preferred derivatives. They are also characterized by better penetration.

The compounds according to the invention are known per se, available commercially or can be obtained by known processes. The literature describes their effect as NO-synthase inhibitors. The acylated compounds can be obtained using the known acylating process.

Particular preference is given to NO-synthase inhibitors according to the invention which contain an arginine radical, and derivatives thereof, in particular as described below.

The invention thus provides in particular for the use, in particular topical use, of one compound or two or more compounds chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention also provides in particular for the use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention further provides cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof.

In each case, the alkyl radicals of the monoalkyl groups or dialkyl groups can have from 1 to 10, preferably from 1 to 6, but in particular 1, 2 or 3, carbon atoms, and can be straight-chain or branched.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of the carboxylic acid group of the arginine with alcohols are also preferred.

Preferred salts are water-soluble salts, e.g. sodium, potassium and ammonium salts. This is also true for the acid addition salts. Suitable acid addition salts are, for example, obtained using inorganic and organic acids. Preference is given to the hydrochlorides, phosphates, sulphates, acetates, caprylates, citrates, lactates, maleates or tartrates.

Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably with monoalcohols. They can be straight-chain or branched and have, for example, from 1 to 12, preferably from 1 to 6, carbon atoms. Preference is given to methanol, ethanol, n-propanol and isopropanol.

The esters are particularly preferred derivatives. They are also characterized by better penetration.

These compounds according to the invention are also known, available commercially or can be obtained by known processes. The literature describes their effect as NO-synthase inhibitors.

Preference is given to the following compounds:
N^G-monomethyl-L-arginine,
N^G-monoethyl-L-arginine,
N^G-nitro-L-arginine,
N^G-nitro-L-arginine methyl ester,
N^G-nitro-L-arginine ethyl ester,
N^G-monomethyl-L-arginine methyl ester,
N^G-monoethyl-L-arginine methyl ester,
N^G-monomethyl-L-arginine ethyl ester
N^G-monoethyl-L-arginine ethyl ester and
N^G, N^G-dimethyl-L-arginine,
N^G, $N^{G'}$-dimethyl-arginine,
N^G, N^G-dimethyl-L-arginine dihydrochloride,
N^G, $N^{G'}$-dimethyl-L-arginine dihydrochloride.

Particular preference is given to the following compounds:
N^G-monomethyl-L-arginine monoacetate (L-NMMA),

N^G-monoethyl-L-arginine monoacetate (L-MEA),
N^G-nitro-L-arginine (L-NNA) and
N^G -Nitro-L-arginine methyl ester hydrochloride (L-NAME).
N^G-nitro-L-arginine methyl ester or
L-NAME is very particularly preferred.

The dermatological and cosmetic topical preparations according to the invention can comprise, as active ingredient, one NO-synthase inhibitor or two or more NO-synthase inhibitors, e.g. one, two or three compounds.

If the preparations comprise two or more of the active ingredients according to the invention, particular preference is given to those preparations which comprise at least one NO-synthase inhibitor containing an arginine radical, in particular one of the abovementioned active ingredients containing an arginine radical.

Particular preference is given to those active ingredient combinations and preparations therewith which contain L-NAME and/or L-NMMA.

The active ingredients which contain an arginine radical can be present in the combinations, for example, in amounts of 10-90% by weight, in particular 30-70% by weight, in each case based on the total weight of the active ingredients.

The compounds according to the invention and the dermatological and cosmetic topical preparations therewith are highly suitable for the treatment and prophylactic treatment of cuperose and of rosacea, in particular of stages I or II.

Surprisingly, the active ingredients and preparations according to the invention exhibit a long-lasting, continuous effect during application. Even after treatment has finished, the skin remains symptom-free and considerably improved for a long time, for example for a period of several weeks.

The cosmetic or dermatological topical preparations according to the invention may be based on formulation bases which are customary per se and serve for the treatment of skin in the sense of a dermatological treatment or a treatment in the cosmetic sense.

The in particular topical use according to the invention of the NO-synthase inhibitors surprisingly leads to a reduction in the cutaneous bloodflow and thus of the erythema. The thereby increased infiltration of leucocytes and other immune cells leads to better healing of the inflamed tissue.

The objects presented are thus achieved.

The active ingredients according to the invention and/or their derivatives are preferably present in the topical cosmetic or dermatological preparations according to the invention in amounts of from 0.001 to 20% by weight, particularly preferably from 0.01 to 10% by weight, but in particular from 0.1 to 5% by weight, in each case based on the total preparation.

Surprisingly, the symptoms of rosacea, in particular the erythema, are alleviated or avoided according to the invention.

Particularly advantageous preparations are also obtained if the active ingredients according to the invention are combined with antioxidants.

The antioxidants according to the invention can be chosen advantageously from the group of customary cosmetic or dermatological antioxidants, in particular from the group consisting of tocopherols and derivatives thereof, particularly α-tocopherol or α-tocopheryl esters, in particular α-tocopheryl acetate, and also sesamol, gallic acid derivatives, such as methyl, ethyl, propyl, amyl, butyl and lauryl gallate, the konyferyl benzoate of benzoin resin, nordihydroguaiac resin acid, nordihydroguaiaretic acid, butylhydroxyanisole, butylhydroxytoluene, ascorbic acid, citric acid, phosphoric acid, lecithin, trihydroxybutyrophenone, carotenes, vitamin A and derivatives thereof, in particular retinyl palmitate, ascorbic acid, ascorbyl palmitate, dilauryl thiodipropionate, distearyl thiodipropionate, monoisopropyl citrate, thiodipropionic acid, EDTA and EDTA derivatives, cysteine, glutathione and esters, uric acid, lipoic acid and esters, carotenes, heavy metal complexing agents such as delta-aminolaevulinic acid and phytic acid and Desferral^{R} (Ciba-Geigy) and flavonoids, e.g. 4^{G}-alpha-glucopyranosyl-rutin.

The cosmetic or dermatological preparations according to the invention preferably comprise from 0.01 to 10% by weight, but in particular from 0.1 to 6% by weight, based on the total weight of the preparations, of one or more substances from the group of antioxidants.

It is preferable to choose the antioxidants according to the invention from the group of flavonoids or of tocopherols and derivatives thereof.

For use, the preparations are applied to the skin in a sufficient amount once or several times daily in the manner customary for cosmetics or dermatological agents.

Particular preference is given to skincare preparations and sunscreen preparations.

Dermatological and cosmetic preparations according to the invention can be in various forms. Thus, for example, aqueous, alcoholic or aqueous-alcoholic solutions, emulsions of the oil-in-water type (O/W), emulsions of the water-in-oil type (W/O), multiple emulsions, e.g. of the water-in-oil-in-water type (W/O/W), gels, hydrodispersions, solid sticks or aerosols can comprise the aforementioned active ingredient combinations. Preference is also given to low-water or water-free ointments and preparations.

The topical preparations according to the invention can comprise customary auxiliaries such as emulsifiers and preservatives.

Preference is also given to those cosmetic and dermatological preparations which are in the form of a sunscreen. Advantageously, these additionally comprise at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment. Particular preference is given to preparations containing one or more UVA filters. Particular preference is given to UVA filters with strong absorption at 340 nm.

However, advantageous preparations are also those which are applied to the skin following exposure to sunlight, i.e. aftersun products. In the case of such preparations, the person skilled in the art must use his discretion as to whether additional UV filter substances should be used or not.

Cosmetic preparations according to the invention for the protection of the skin against UV rays can be in various forms, as are, for example, customarily used for this type of preparations. Thus, for example, they can be aqueous, alcoholic or aqueous-alcoholic solutions, emulsions of the water-in-oil type (W/O) or of the oil-in-water type (O/W), or multiple emulsions, for example of the water-in-

oil-in-water type (W/O/W), gels, hydrodispersions, oils, solid sticks or else aerosols.

The topical preparations according to the invention can comprise dermatological and cosmetic auxiliaries, as are customarily used in such preparations, e.g. preservatives, bactericides, perfumes, antifoams, dyes, pigments which have a colouring effect, thickeners, surface-active substances, emulsifiers, emollients, moisturizers and/or humectants, fats, oils, waxes, or other customary constituents of a cosmetic formulation such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivatives.

If the cosmetic or dermatological preparation is a solution or lotion, the solvents used may be:

- water or aqueous solutions;

- oils, such as triglycerides of capric or of caprylic acid, but preferably castor oil;

- fats, waxes and other natural and synthetic fatty substances, preferably esters of fatty acids with alcohols of low carbon number, e.g. with isopropanol, propylene glycol or glycerol, or esters of fatty alcohols with alkanoic acids of low carbon number or with fatty acids;

- alcohols, diols or polyols of low carbon number, and ethers thereof, preferably ethanol, isopropanol, propylene glycol, glycerol, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl or monobutyl ether, diethylene glycol monomethyl or monoethyl ether and analogous products.

In particular, mixtures of the abovementioned solvents are used. In the case of alcoholic solvents, water can be an additional constituent.

Oils or emulsions according to the invention, for example in the form of a sunscreen cream, a sunscreen lotion or a sunscreen milk, are advantageous and comprise, for example, the specified fats, oils, waxes and other fatty substances, and water and an emulsifier, as is customarily used for this type of formulation.

Cosmetic and dermatological preparations for the treatment and care of the skin can be in the form of gels which, in addition to the active ingredients and the solvents customarily used therefor, also comprise organic thickeners, e.g. gum arabic, xanthan gum, sodium alginate, cellulose derivatives, preferably methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or inorganic thickeners, e.g. aluminium silicates such as, for example, bentonites, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. The thickener is present in the gel, for example, in an amount between 0.1 and 30% by weight, preferably between 0.5 and 15% by weight.

Gels according to the invention usually comprise alcohols of low carbon number, e.g. ethanol, isopropanol, 1,2-propanediol, glycerol and water, or an abovementioned oil in the presence of a thickener which, in the case of oily-alcoholic gels, is preferably silicon dioxide or an aluminium silicate, and in the case of aqueous-alcoholic or alcoholic gels, is preferably a polyacrylate.

Hydrodispersions are dispersions of a liquid, semisolid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase.

In contrast to O/W emulsions, which are characterized by a similar phase arrangement, hydrodispersions are, however, essentially free from emulsifiers. Hydrodispersions, like emulsions, are metastable systems and have a propensity to convert to a state of two coherent discrete phases. In emulsions, the choice of a suitable emulsifier prevents phase separation.

In the case of hydrodispersions of a liquid lipid phase in an outer aqueous phase, the stability of such a system can, for example, be ensured by building up a gel structure in the aqueous phase, in which structure the lipid droplets are suspended in stable form.

Solid sticks according to the invention can, for example, comprise natural or synthetic waxes, fatty alcohols or fatty acid esters. Preference is given to lipcare sticks.

Suitable propellants for cosmetic or dermatological preparations which can be sprayed from aerosol containers are the customary known readily volatile, liquefied propellants, for example hydrocarbons (propane, butane, isobutane),

which can be used alone or mixed with one another. Compressed air can also be used advantageously.

The person skilled in the art is of course aware that there are propellants which are nontoxic per se which would in principle be suitable for the present invention, but which should nevertheless be avoided because of an unacceptable impact on the environment or other accompanying circumstances, in particular fluorinated hydrocarbons and fluorochlorocarbons (CFCs).

Preferably, the preparations according to the invention can also comprise substances which absorb UV radiation in the UVB region, the total amount of filter substances being, for example, from 0.1% by weight to 30% by weight, preferably from 0.5 to 10% by weight, in particular from 1 to 6% by weight, based on the total weight of the preparation, in order to make available preparations which protect the skin against the entire range of ultraviolet radiation. They can also serve as sunscreens.

The UVB filters can be oil-soluble or water-soluble. Examples of oil-soluble substances are:

- 3-benzylidenecamphor derivatives, preferably
  3-(4-methylbenzylidene)camphor, 3-benzylidenecamphor;

- 4-aminobenzoic acid derivatives, preferably
  2-ethylhexyl 4-(dimethylamino) benzoate,
  amyl 4-(dimethylamino)benzoate;

- esters of cinnamic acid, preferably
  2-ethylhexyl 4-methoxycinnamate,
  isopentyl 4-methoxycinnamate;

- esters of salicylic acid, preferably
  2-ethylhexyl salicylate,
  4-isopropylbenzyl salicylate,
  homomenthyl salicylate;

- derivatives of benzophenone, preferably
  2-hydroxy-4-methoxybenzophenone,

2-hydroxy-4-methoxy-4'-methylbenzophenone,
2,2'-dihydroxy-4-methoxybenzophenone;

- esters of benzalmalonic acid, preferably
di(2-ethylhexyl) 4-methoxybenzalmalonate;

- 2,4,6-trianilino(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5-triazine.

Examples of water-soluble substances are:

- salts of 2-phenylbenzimidazole-5-sulphonic acid such as its sodium, potassium or triethanolammonium salt,
and the sulphonic acid itself;

- sulphonic acid derivatives of benzophenones, preferably
2-hydroxy-4-methoxybenzophenone-5-sulphonic acid and its salts;

- sulphonic acid derivatives of 3-benzylidenecamphor, such as
e.g. 4-(2-oxo-3-bornylidenemethyl)benzenesulphonic acid,
2-methyl-5-(2-oxo-3-bornylidenemethyl)sulphonic acid and its salts.

The invention also provides the combination of active ingredients according to the invention with one or more UVA and/or UVB filters, and cosmetic or dermatological preparations according to the invention which also comprise one or more UVA and/or UVB filters.

It can also be particularly advantageous to combine the active ingredients with UVA filters which are customarily present in cosmetic and/or dermatological preparations. The substances are preferably derivatives of dibenzoylmethane, in particular 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl)propane-1,3-dione. These combinations and preparations which comprise these combinations are also provided by the invention. The amounts which can be used are those given for the UVB combination.

Advantageous preparations are also obtained if the active ingredients according to the invention are combined with UVA and UVB filters.

Combinations of the active ingredients according to the invention with one or more antioxidants and one or more UVA filters and/or one or more UVB filters are also particularly advantageous according to the invention.

The cosmetic or dermatological preparations can also comprise inorganic pigments which are customarily used in cosmetics for protecting the skin against UV rays. These are oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminium, cerium and mixtures thereof, and modifications in which the oxides are the active agents. Particularly preferably, they are pigments based on titanium dioxide.

The invention also provides the process for the preparation of the topical preparations according to the invention, which is characterized in that the active ingredients are incorporated into cosmetic or dermatological formulations in a manner known per se.

All quantities, proportions and percentages are, unless stated otherwise, based on the weight and the total amount or on the total weight of the preparations.

The examples below serve to illustrate the present invention without limiting it.

In the examples, the following compounds are used:

N^G-monomethyl-L-arginine monoacetate (L-NMMA),
N^G-monoethyl-L-arginine monoacetate (L-MEA),
N^G-nitro-L-arginine (L-NNA),
N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME).

Example 1

Sun gel (transparent)

	% by weight
L-NAME	1
Benzophenone-4	0.5
Phenylbenzimidazolesulphonic acid	1.3
Acrylamide/sodium acrylate copolymer	1.6
Ethanol	5.0
Glycerol	15.0
NaOH (15% strength)	q.s.
Perfume, preservative	q.s.
Water, demin. (demineralized)	ad 100.0

Example 2

Hydrodispersion

	% by weight
L-NMMA	5.0
Phenyltrimethicone	1.0
Carbomer (Carbopol 981)	1.0
Hydroxypropylmethylcellulose	0.2
Butylene glycol	3.0
Tromethamine	q.s.
EDTA solution (14% strength)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 3

O/W sun milk

	% by weight
L-MEA	2.5
Urea	5.0
Octyl methoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearyl alcohol + PEG-40 castor oil + sodium cetearyl sulphate	2.5
Glyceryl lanolate	1.0
Laurylmethicone copolyol	0.5
Mineral oil (GP 9)	5.0
Caprylic/capric triglycerides	5.0
Acrylamide-sodium acrylate copolymer	0.3
Cyclomethicone	2.0
TiO_2	1.0
Glycerol	3.0
EDTA solution (14% strength)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 4

W/O care lotion

	% by weight
L-NNA, HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 5

O/W face-care cream

	% by weight
L-NMMA	2.5
PEG-5 glyceryl stearate	2.00
Glyceryl stearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglycerides	3.00
Cetyl alcohol	3.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopheryl acetate	0.50
Glycerol	4.00
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 6

W/O cream

	% by weight
L-NMMA	2.5
PEG-22 dodecyl glycol copolymer	3.0
Cetyl dimethicone copolyol	2.0
Cyclomethicone	4.0
Mineral oil (GP 9)	4.0
Caprylic/capric triglycerides	4.0
Glycerol	4.00
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 7

Aftersun lotion	% by weight
L-NAME	5.0
Cetearyl alcohol + PEG-40 castor oil + sodium cetearyl sulphate	2.50
Glyceryl stearate SE	0.60
Mineral oil (GP 9)	4.00
Caprylic/capric triglycerides	2.00
Shea butter	2.00
Avocado oil	2.00
Tocopheryl acetate	3.00
Acrylamide-sodium acrylate copolymer	0.30
Glycerol	4.00
Hyaluronic acid	0.05
Bisabolol	0.05
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 8

Shower milk	% by weight
L-MEA	5.0
Sodium laureth sulphate	11
Cocamidopropyl betaine	5
Cocamide DEA	1
PEG-8	1
Soybean oil	1
Citric acid	0.1
Sodium chloride	0.2
Fragrance	0.1
Water, demin.	ad 100.00

Example 9

Care stick

	% by weight
1,2-Propylene glycol	11.0
Oleyl alcohol	14.0
Eosin dyes	3.0
Stearamide MEA (Rewomid S 280)	10.0
Beeswax	10.0
Glycerol monostearate	10.0
Cetyl alcohol	10.0
Ceresine	8.0
Stearyl heptanoate (CL-solid)	6.0
Lanolin anhydr.	6.0
Pigments and coloured lakes	6.0
Perfume oil	1.0
L-NAME	5.0

Example 10

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and) octyldodecanol (and) carnauba (and) candelilla wax (and) microcrystalline (and) cetyl alcohol (and) beeswax (and) mineral oil	
Cutina LM (Henkel)	65
Caprylic/capric triglycerides (Myristol 318)	20
Pigment colours	3.0
Titanium dioxide	7.0
L-NMMA	4.0
L-NIO	1.0

Example 11

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and) octyldodecanol (and) carnauba (and) candelilla wax (and) microcrystalline wax (and) cetyl alcohol (and) beeswax (and) mineral oil Cutina LM (Henkel)	78.0
Octyldodecanol (Eutanol G)	15.0
Colour pigments	2.0
L-NMMA	4.0
L-NIL	1.0

Example 12

W/O care lotion

	% by weight
2-Iminobiotin	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 13

W/O care lotion

	% by weight
L-NIO-HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 14

W/O care lotion

	% by weight
S-Methylisothiourea sulphate	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 15

W/O care lotion

	% by weight
S-Methyl-L-thiocitrulline 2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 16

W/O care lotion

	% by weight
L-NIL-2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 17

W/O Care lotion

	% by weight
7-Nitroindazole	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 18

W/O Care lotion

	% by weight
PBITU-2HBr	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 19

W/O Care lotion

	% by weight
L-Thiocitrulline 2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 20

Sun gel (transparent)

	% by weight
Alpha-N-acetyl-L-NAME (with monoacetylated amino group on the alpha-carbon atom of L-NAME)	1
Benzophenone-4	0.5
Phenylbenzimidazolesulphonic acid	1.3
Acrylamide/sodium acrylate copolymer	1.6
Ethanol	5.0
Glycerol	15.0
NaOH (15% strength)	q.s.
Perfume, preservative	q.s.
Water, demin. (demineralized)	ad 100.0

Example 21

Preparation of alpha-N-acetyl-L-NAME (in accordance with Example 20)

1 equivalent of L-NAME hydrochloride is dissolved in methanol/Na methoxide (1 equivalent, 8 ml of methanol/mmol) under nitrogen and stirred with 1.5 equivalents of acetic anhydride for 2 h. It is then worked up as usual under aqueous conditions and admixed with saturated NaCl solution and extracted with ethyl acetate and dried with Mg sulphate. The solvent is stripped off to give pure alpha-N-acetyl-L-NAME, yield 71%.

^{1}H-NMR spectrum: 1.60, multiplet, 4 H; 1.90, singulet, 3 H; 3.15, triplet, 2 H; 3.60, singulet, 3H of the acetyl-Me group; 4.35, triplet, 1 H.

alpha-N-Acetyl-N^G-monomethyl-L-arginine monoacetate (alpha-N-acetyl-L-NMMA),
alpha-N-acetyl-N^G-monoethyl-L-arginine monoacetate (alpha-N-acetyl-L-MEA),
alpha-N-acetyl-N^G-nitro-L-arginine (alpha-N-acetyl-L-NNA),
alpha-N-acetyl-N^G-nitro-L-arginine methyl ester (alpha-N-acetyl-L-NAME) are obtained in an analogous way.

The N-acyl compounds according to the invention of the NO-synthase inhibitors which optionally carry one or more amino groups or a guanidine group are novel, in particular the acetyl compounds, e.g. the monoacetyl compounds, in particular those acyl compounds or acetyl compounds of amino groups or alpha-carbon amino groups of amino acids. Further preferred acyl radicals are aromatically substituted carbonyl, for example benzoyl.

Acyl compounds according to the invention are obtained by customary acylation processes, e.g. by reaction of [lacuna] with acid halides or acid anhydrides, optionally with the addition of solvents and bases, e.g. triethylamine or alkoxides. For the monoacyl compounds, equivalent amounts of NO-synthase inhibitors and acylating agents are preferred. For polyacylated compounds, for example, correspondingly higher equivalent amounts are used, it being possible, for example, where appropriate, to react other amino groups and the guanidino group.

Patent claims

1. Use of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

2. Use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

3. Cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof.

4. Use according to Claim 2, characterized in that the preparations comprise at least one antioxidant.

5. Use according to Claim 2, characterized in that the preparations comprise at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.

6. Use according to Claim 2, characterized in that the preparations comprise at least one antioxidant and at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.

7. Use of one compound or two or more compounds according to Claim 1, chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

8. Use of cosmetic or dermatological topical preparations according to Claim 2, with a content of one compound or two or more compounds chosen from the group N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

9. Cosmetic or dermatological topical preparations according to Claim 3, with a content of one compound or two or more compounds chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof.

10. Use or preparation according to Claims 7-9, characterized in that N^G-nitro-L-arginine methyl ester or N^G-nitro-L-arginine methyl ester hydrochloride is used.

11. Use according to Claim 8, characterized in that the preparations comprise at least one antioxidant.

12. Use according to Claim 8, characterized in that the preparations comprise at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.

13. Use according to Claim 8, characterized in that the preparations comprise at least one antioxidant and at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment.

14. Use of one compound or two or more compounds chosen from the group of NO-synthase inhibitors which contain an arginine radical, and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

15. Use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors which contain an arginine radical, and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

16. Cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors which contain an arginine radical, and derivatives thereof.

17. NO-Synthase inhibitor containing one or more acylated amino groups, in particular monoacylated amino groups.

Abstract

The invention relates to the use, in particular topical use, of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

Beiersdorf 569-WCG
6713-Dr.Lt-ka

09/367748

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : DIEMBECK, et al.

Serial No. : 09/367,748

Filed : August 19, 1999

For : PREPARATIONS FOR THE TREATMENT OF ROSACEA

Art Unit : Not Assigned

Examiner : Not Assigned

November 17, 1999

Hon. Assistant Commissioner
for Patents
Washington, D. C. 20231

NOTICE OF CHANGE OF FIRM NAME

Sir:

Please note that the name of the firm of the undersigned has changed to:

NORRIS, McLAUGHLIN & MARCUS, P.A.

Please address all future correspondence in this application to:

William C. Gerstenzang
NORRIS, McLAUGHLIN & MARCUS, P.A.
660 White Plains Road
Tarrytown, New York 10591-5144

Respectfully submitted,

NORRIS, McLAUGHLIN & MARCUS, P.A.

By _____
William C. Gerstenzang
Reg. No. 27,552

WCG:kts

660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

09/367748

ATTORNEY DOCKET No.:Beiersdorf 569-WCG
6713-Dr.Lt-ka

COMBINATION DECLARATION & POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PREPARATIONS FOR THE TREATMENT OF ROSACEA, the specification of which is attached hereto.

was filed on August 19, 1999 as application Serial No. 09/367,748 .

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
197 06 581.3 (Number)	Germany (Country)	February 21, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no
197 11 565.9 (Number)	Germany (Country)	March 20, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code

09/367748

ATTORNEY DOCKET No.:Beiersdorf 569-WCG
6713-Dr.Lt-ka

COMBINATION DECLARATION & POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PREPARATIONS FOR THE TREATMENT OF ROSACEA, the specification of which is attached hereto.

was filed on August 19, 1999 as application Serial No. 09/367,748 .

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
197 06 581.3 (Number)	Germany (Country)	February 21, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no
197 11 565.9 (Number)	Germany (Country)	March 20, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code

of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. 17,232; Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802 and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York 10591; Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Carmella A. O'Gorman, Reg. No. 33,749 and Stephen G. Ryan, Reg. No. 39,015 all of 660 White Plains Road, Tarrytown, New York 10591-5144, my attorneys with full power of substitution and revocation.

SEND CORRESPONDENCE TO:
SPRUNG KRAMER SCHAEFER & BRISCOE
660 WHITE PLAINS ROAD
TARRYTOWN, N.Y. 10591-5144

DIRECT TELEPHONE CALLS TO:
(914) 332-1700

FULL NAME OF SOLE OR FIRST INVENTOR: Walter Diembeck

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany

FULL NAME OF SECOND INVENTOR: Udo Hoppe

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany

ATTORNEY DOCKET No.:Beiersdorf 569-WCG
6713-Dr.Lt-ka

COMBINATION DECLARATION & POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PREPARATIONS FOR THE TREATMENT OF ROSACEA, the specification of which is attached hereto.

was filed on August 19, 1999 as application Serial No. 09/367,748 .

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
197 06 581.3 (Number)	Germany (Country)	February 21, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no
197 11 565.9 (Number)	Germany (Country)	March 20, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code

of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. ~~17,232;~~ Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802 and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York ~~10591;~~ Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Carmella A. O'Gorman, Reg. No. ~~33,749~~ and Stephen G. Ryan, Reg. No. 39,015 all of 660 White Plains Road, Tarrytown, New York 10591-5144, my attorneys with full power of substitution and revocation.

~~SEND CORRESPONDENCE TO:~~
SPRUNG KRAMER SCHAEFER & BRISCOE
660 WHITE PLAINS ROAD
TARRYTOWN, N.Y. 10591-5144

DIRECT TELEPHONE CALLS TO:
(914) 332-1700

FULL NAME OF SOLE OR FIRST INVENTOR: Walter Diembeck

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany

FULL NAME OF SECOND INVENTOR: Udo Hoppe

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany

ATTORNEY DOCKET No.:Beiersdorf 569-WCG
6713-Dr.Lt-ka

COMBINATION DECLARATION & POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PREPARATIONS FOR THE TREATMENT OF ROSACEA, the specification of which is attached hereto.

was filed on August 19, 1999 as application Serial No. 09/367,748 .

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
197 06 581.3 (Number)	Germany (Country)	February 21, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no
197 11 565.9 (Number)	Germany (Country)	March 20, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code

FULL NAME OF THIRD INVENTOR: Birgit Salzer

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alsterkamp 19, D-20149 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alsterkamp 19, D-20149 Hamburg, Germany

FULL NAME OF FOURTH INVENTOR: Gerhard Sauermann

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Hambrook 14, D-24649 Wiemersdorf, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Hambrook 14, D-24649 Wiemersdorf, Germany

FULL NAME OF FIFTH INVENTOR: Volker Steinkraus

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Fontanestrasse 18, D-22609 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Fontanestrasse 18, D-22609 Hamburg, Germany

ATTORNEY DOCKET No.:Beiersdorf 569-WCG
6713-Dr.Lt-ka

COMBINATION DECLARATION & POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PREPARATIONS FOR THE TREATMENT OF ROSACEA, the specification of which is attached hereto.

was filed on August 19, 1999 as application Serial No. 09/367,748 .

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
197 06 581.3 (Number)	Germany (Country)	February 21, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no
197 11 565.9 (Number)	Germany (Country)	March 20, 1997 (Day/Month/Yr. Filed)	[X] yes [ ]no

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code

FULL NAME OF THIRD INVENTOR: Birgit Salzer

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alsterkamp 19, D-20149 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alsterkamp 19, D-20149 Hamburg, Germany

FULL NAME OF FOURTH INVENTOR: Gerhard Sauermann

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Hambrook 14, D-24649 Wiemersdorf, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Hambrook 14, D-24649 Wiemersdorf, Germany

FULL NAME OF FIFTH INVENTOR: Volker Steinkraus

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Fontanestrasse 18, D-22609 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Fontanestrasse 18, D-22609 Hamburg, Germany

of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. 17,232; Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802 and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York 10591; Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Carmella A. O'Gorman, Reg. No. 33,749 and Stephen G. Ryan, Reg. No. 39,015 all of 660 White Plains Road, Tarrytown, New York 10591-5144, my attorneys with full power of substitution and revocation.

SEND CORRESPONDENCE TO:
SPRUNG KRAMER SCHAEFER & BRISCOE
660 WHITE PLAINS ROAD
TARRYTOWN, N.Y. 10591-5144

DIRECT TELEPHONE CALLS TO:
(914) 332-1700

FULL NAME OF SOLE OR FIRST INVENTOR: Walter Diembeck

INVENTOR'S SIGNATURE: Walter Diembeck DATE: 26/10/99

RESIDENCE: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany CITIZENSHIP: German DEX

POST OFFICE ADDRESS: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany

FULL NAME OF SECOND INVENTOR: Udo Hoppe

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany

of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. 17,232; Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802 and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York 10591; Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Carmella A. O'Gorman, Reg. No. 33,749 and Stephen G. Ryan, Reg. No. 39,015 all of 660 White Plains Road, Tarrytown, New York 10591-5144, my attorneys with full power of substitution and revocation.

SEND CORRESPONDENCE TO:
SPRUNG KRAMER SCHAEFER & BRISCOE
660 WHITE PLAINS ROAD
TARRYTOWN, N.Y. 10591-5144

DIRECT TELEPHONE CALLS TO:
(914) 332-1700

FULL NAME OF SOLE OR FIRST INVENTOR: Walter Diembeck

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany

FULL NAME OF SECOND INVENTOR: Udo Hoppe

INVENTOR'S SIGNATURE: Udo Hoppe DATE: 16-09-99

RESIDENCE: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany

of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Arnold Sprung, Reg. No. ~~17,232;~~ Nathaniel D. Kramer, Reg. No. 25,350; Ira J. Schaefer, Reg. No. 26,802 and Esther Steinhauer, Reg. No. 40,255 all of 120 White Plains Road, Tarrytown, New York 10591; Kurt G. Briscoe, Reg. No. 33,141; William C. Gerstenzang, Reg. No. 27,552; Carmella A. O'Gorman, Reg. No. 33,749 and Stephen G. Ryan, Reg. No. 39,015 all of 660 White Plains Road, Tarrytown, New York 10591-5144, my attorneys with full power of substitution and revocation.

SEND CORRESPONDENCE TO:
SPRUNG KRAMER SCHAEFER & BRISCOE
660 WHITE PLAINS ROAD
TARRYTOWN, N.Y. 10591-5144

DIRECT TELEPHONE CALLS TO:
(914) 332-1700

FULL NAME OF SOLE OR FIRST INVENTOR: Walter Diembeck

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Osterfeldstrasse 79 d, D-22529 Hamburg, Germany

FULL NAME OF SECOND INVENTOR: Udo Hoppe

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alte Wassermühle, Mühlenholz 1, D-24598 Heidmühlen, Germany

3W FULL NAME OF THIRD INVENTOR: Birgit Salzer

INVENTOR'S SIGNATURE: B. Salzer DATE: 17.9.99

RESIDENCE: Alsterkamp 19, D-20149 Hamburg, Germany DEX CITIZENSHIP: German

POST OFFICE ADDRESS: Alsterkamp 19, D-20149 Hamburg, Germany

FULL NAME OF FOURTH INVENTOR: Gerhard Sauermann

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Hambrook 14, D-24649 Wiemersdorf, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Hambrook 14, D-24649 Wiemersdorf, Germany

FULL NAME OF FIFTH INVENTOR: Volker Steinkraus

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Fontanestrasse 18, D-22609 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Fontanestrasse 18, D-22609 Hamburg, Germany

FULL NAME OF THIRD INVENTOR: Birgit Salzer

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alsterkamp 19, D-20149 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alsterkamp 19, D-20149 Hamburg, Germany

40 FULL NAME OF FOURTH INVENTOR: Gerhard Sauermann

INVENTOR'S SIGNATURE: Gerhard Sauermann DATE: 11-11-1999

RESIDENCE: Hambrook 14, D-24649 Wiemersdorf, Germany DX CITIZENSHIP: German

POST OFFICE ADDRESS: Hambrook 14, D-24649 Wiemersdorf, Germany

FULL NAME OF FIFTH INVENTOR: Volker Steinkraus

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Fontanestrasse 18, D-22609 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Fontanestrasse 18, D-22609 Hamburg, Germany

FULL NAME OF THIRD INVENTOR: Birgit Salzer

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Alsterkamp 19, D-20149 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Alsterkamp 19, D-20149 Hamburg, Germany

FULL NAME OF FOURTH INVENTOR: Gerhard Sauermann

INVENTOR'S SIGNATURE: _____ DATE: _____

RESIDENCE: Hambrook 14, D-24649 Wiemersdorf, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Hambrook 14, D-24649 Wiemersdorf, Germany

FULL NAME OF FIFTH INVENTOR: Volker Steinkraus

INVENTOR'S SIGNATURE: V. Steinkraus DATE: 21.9.99

RESIDENCE: Fontanestrasse 18, D-22609 Hamburg, Germany CITIZENSHIP: German

POST OFFICE ADDRESS: Fontanestrasse 18, D-22609 Hamburg, Germany